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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :
ULRICH BOCKELMANN, ET AL. : EXAMINER: CROW, R. T.
SERIAL NO: 10/501,772 :
FILED: APRIL 25, 2005 : GROUP ART UNIT: 1634
FOR: DETECTION OF MOLECULAR :
PROBES FIXED TO AN ACTIVE ZONE
OF A SENSOR

DECLARATION UNDER 37 C.F.R. § 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

1. Now comes Prof. Dr. Peter Fromherz, residing at the Max-Planck Institute for Biochemistry, Department of Membrane and Neurophysics, Am Klopferspitz 18, D 82152 Martinsried_Munich, Germany.

2. I am a director at the Max Planck Institute for Biochemistry in Martinsried/Munich and a professor of Experimental Biophysics in the Physical Faculty of the Technical University of Munich. In 1981, I became a full professor of Experimental Physics at the University of Ulm. Since 1994, I have been a scientific member of the Max Planck Society. My present research interests are the interfacing of semiconductor chips with neuronal systems and the development of voltage sensitive dyes for brain research.

3. I have received a Diploma in Chemistry in 1966 at the Karlsruhe Institute of Technology in Karlsruhe/Germany, and a PhD in Physical Chemistry in 1969 at the University Marburg, in Marburg/Germany.

4. The opinions herein are my own, and I have no stake in the outcome of any proceedings or any related litigation for this application or any other application of the assignee.

5. I have read all of the specification of application serial number 10/501,772 (hereinafter, “the present application”) and the claims as presented in the amendment filed on August 27, 2009. I have also fully read the Office Actions issued on December 7, 2009 and May 27, 2010. I have also fully read Lindsay et al. (U.S. Patent Publication No. 2004/0238379, hereinafter Lindsay), Kariyone et al. (U.S. Patent No. 5,242,793, hereinafter Kariyone), and Hafeman et al. (U.S. Patent No. 5,164,319, hereinafter Hafeman).

6. I have been told that a claim in a patent application is obvious if the difference between the subject matter to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

7. A person having ordinary skill in the art to which the claimed invention of the present application pertains possesses an academic education combining knowledge in the fields pertaining to the present application, in particular semiconductor science and technology, biophysics, biochemistry, electrostatics and chemistry of silica surfaces in contact with aqueous solutions.

8. Lindsay is directed to a method for electronically detecting hybridization of a probe nucleic acid and a target nucleic acid. (Lindsay, Abstract.) For his method, Lindsay explains that a back-gated field effect transistor FET is used, where a layer of silicon 10 is provided on a buried oxide layer 20, located on a silicon wafer or substrate 30, where a source 40 and drain 50 and a n-channel 65 are provided in the silicon 10. (Lindsay, p. 2, ¶¶ [0019]-[0020], Fig. 1a.).

9. Lindsay also explains that when the FET is operated with a buffer including a DNA on the upper surface 75 for a measurement, an applied drain-source bias voltage 70 is kept constant, and a backgate voltage 60 V_{bg} is grounded, so that his silicon wafer or substrate 30 is also grounded. (Lindsay, p. 4, ¶ [0036]-[0037], Fig. 7.)

10. With the configuration of Lindsay's FET, it is *not possible* to fix both the potential of the buffer (fluid) and the gate voltage. The buffer (or fluid) is electrically isolated from the semiconductor structure by oxide layer 110 and passivating layer 100. Electrical connections are provided only to the solid state parts of the device in Lindsay.

11. Lindsay fails to disclose the following feature of Claim 1 of the present application: "fixing a potential of the electrolyte solution which covers said active zones with an electrode that applies a gate source voltage to the field effect transistors, the electrode being immersed in said electrolyte solution."

12. There is a fundamental difference between Claim 1 of the present application and Lindsay in the way the electrical potential is applied to and distributed between the different parts of the structure. There is a significant distinction among electrical potentials in liquid, at the liquid-solid interface, and in the semiconductor. At the time the invention of Claim 1 in the present application was made, the energy alignment and band bendings at the semiconductor liquid interface were important topics subject to significant controversy. For instance, people from the solid state physics field use different terminology and intellectual concepts than people from the electrochemistry fields. A broadly accepted conceptual framework bridging the different fields is still lacking. Finding an appropriate mode of detection is thus difficult, since it requires a combination of non-trivial insights from different fields, in particular semiconductor device physics and technology, semiconductor surface science, electrostatics and chemistry of silica surfaces in contact with aqueous solutions.

13. In Lindsay, the inversion layer is defined by a back-gate, which is a pure semiconductor device configuration fixing the working point of a FET. Lindsay does not clarify the effect of the solution on this working point, or how the detection is supposed to function. This is because the electrostatic potential of the semiconductor surface facing the fluid is not well defined in Lindsay. Although Lindsay's paragraph 39 describes how the source current drops after the hybridizing target DNA is introduced, the physical mechanism of the proposed detection is not clear. In fact, the electrostatic potential of the surface, and in turn the electric field on the channel 65, is not well defined in the Lindsay configuration. To achieve a reproducible detection, the skilled person in the art needs to control, at a molecular level, the charging state of the surface. To the best of my knowledge, there was no method to achieve such control at the date of the invention, other than what is disclosed in Applicants' specification.

14. Claim 1 of the present application uses a reference electrode in the solution to fix the potential of the electrolyte solution with respect to the semiconductor on the liquid side of the liquid-solid interface. This aspect plays a fundamentally different role than the back gate electrode in Lindsay, and accounts for the above-mentioned liquid-solid interface issue, which Lindsay fails to address.

15. Unlike the invention defined by Claim 1 of the present application, the back gate electrode of Lindsay does not fix a potential of the electrolyte solution. Lindsay fails to consider the coupling of the active regions to the liquid, and thus to consider the role this coupling plays in biomolecule detection. This difference is profound and is not a trivial difference between the configuration of Lindsay and Claim 1 of the present application. Lindsay's back gate simply is a semiconductor device configuration to adjust the drain current, known by specialists in semiconductor device physics and technology. The electrode of Claim 1 does not only adjust the drain current. Its most important role is to provide a

common electrostatic potential to the different active regions of the array. In the present application the electrode thus plays an entirely new and important role, allowing for reproducible differential detection.

16. Kariyone describes an electrochemistry approach, based on electrodes that sustain electrical current. The electrodes have an electrically conductive base, and a selectively permeable membrane which is produced by forming a membrane from a mixed solution comprising (a) albumin, (b) at least one type of cross-linking agent and (c) chitosan. (See Kariyone, Abstract.) The electrode is used to detect consumption of oxygen or formation of hydrogen peroxide in biochemical reactions by an immobilized enzyme. (Kariyone, col. 1, ll. 56-60.) In order to avoid the detection of other substances, such as ascorbic acid, Kariyone explains that a selective permeable membrane can be placed between the immobilized enzyme and the hydrogen peroxide electrode. (Kariyone, col. 1, l. 64, to col. 2, l. 4.)

17. Regarding Kariyone's measurement system, it is explained that a working electrode E1-E6 used together with comparison electrodes C1-C6 to detect redox reaction, and a counter electrode 7 can balance the electrons added or removed by the working electrodes E1-E6, and a reference electrode 8 that controls the working electrodes E1-E6 potential. (See Kariyone, col. 9, ll. 2-28, Fig. 1.) To perform the measurements with electrodes E1-E6 and C1-C6, Kariyone explains that that these electrodes are *not used simultaneously*, but are used from one experiment to the next, in twelve successive experiments. (See Kariyone, examples, from col. 9 to col. 17.) Kariyone also does not use any transistors to perform his measurements, but applies electrical fields between two electrodes. (Kariyone, col. 9.) Consequently, Kariyone does not teach initial detection of the immobilization of a probe before detection of hybridization of targets to the probes, and does not imply an initial detection of the immobilization of a probe.

18. Lindsay is directed to a measurement system using a FET device, where fluids are placed on a channel region and a change in is detected, and Kariyone is using immobilized enzymes between two electrodes E1-E6 and C1-C6 to measure electric current in a solution with electrochemistry, a selective membrane, and an enzyme membrane. Thus, Lindsay and Kariyone describe substantially different measurement principles, and a person having ordinary skill in the art would not look to Kariyone as basis to modify the device of Lindsay.

19. Although Lindsay and Kariyone both describing detecting molecules, a person having ordinary skill in the art, at the time the invention of Claim 1 in the present application was made, would not have thought to combine these two very disparate measurement principles. Furthermore, the fact that measurements of current are used in both Lindsay and Kariyone to detect the fixation of a molecule does not mean that Lindsay and Kariyone are analogous.

20. There are several differences between Lindsay and Kariyone. In Kariyone, chemical reactions generate charge carriers in a solution and electrical currents flowing through the membranes are measured. In Lindsay, there are no chemical reactions, no membranes and no electrical current flow in the solution. Indeed, the field of electrochemistry (see Kariyone) is very different from the field of the present application, which performs electronic detection with FET transistors. A person having ordinary skill in the art, at the time the invention defined by Claim 1 of the present application was made, would consider Lindsay and Kariyone to be non-analogous art.

21. In addition, the electrodes of Kariyone cannot be readily included in the device of Lindsay. The electrochemical detection with electrical current in solution and the electrostatic detection are incompatible, and a person having ordinary skill in the art would not combine the two entirely different approaches. Claim 1 of the present application has

nothing to do with a combination of Kariyone and Lindsay. In any case, to include the electrodes of Kariyone in the device of Lindsay would have required knowledge and skill beyond the level of the person having ordinary skill in the art, and would have required a substantial reconstruction of the method of Lindsay that a person having ordinary skill in the art could not make.

22. The following statement at pages 4-5 of the Office Action issued December 7, 2009 is *incorrect*:

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method as taught by Lindsay to further comprise the initial detection of the immobilization of a probe as taught by Kariyone et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of providing a quality control indicator for each of the sensors of the method as a result of confirming the stable immobilization of the probe to the surface as explicitly taught by Kariyone et al. (column 17, lines 1-10). In addition, it would have been obvious to the ordinary skilled artisan that the known technique of using the initial detection of the immobilization of a probe as taught by Kariyone et al could have been applied to the method of Lindsay et al with predictable results because the known technique of using the initial detection of the immobilization of a probe as taught by Kariyone et al predictably results in verification of stably immobilized probes.

23. Hafeman is not directed to any field-effect transistors, but is directed to a capacitively operated device for detecting particles having an electrode 10 and a counter-electrode 14. (Hafeman, Abstract, Fig. 1.) Hafeman's electrode 10 is made of a substrate that has doped semiconductor material, for example n type of p type, with regions or "pixels" that are electrically isolated from each other. Moreover, in Hafeman, these regions can be similarly doped, or oppositely doped, and when they are similarly doped, there will be a positively doped barrier 17 separating each of the regions from each other. (Hafeman, from col. 14, l. 65 to col. 15, l. 1.) In addition, Hafeman's electrode 10 is coated with a uniform

insulating layer and the particle detection is done by measuring the capacitance between the electrodes 10 and 14.

24. The electrodes of Hafeman play a different role than the electrode in Claim 1 of the present application. In Hafeman, detection is done by impedance measurements, a capacitive measurement technique that requires at least two opposing electrodes to sustain an AC current. The electrode configuration described by Hafeman is often employed in this field to eliminate potential differences associated with electrochemistry at the current electrodes. (see for instance Bard&Faulkner, Electrochemical Methods: Fundamentals and Applications, excerpt submitted herewith.) The electrode configuration of Hafeman has nothing to do with the FET configurations of Lindsay or the invention of Claim 1 in the present application. A person of ordinary skill in the art, at the time the invention defined by Claim 1 of the present application was made, would not have combined the teachings of Hafeman with Lindsay.

25. Hafeman does not teach a person of ordinary skill in the art, at the time the invention of Claim 1 of the present application was made, to modify Lindsay to fix the potential of the active zones with an electrode that applies a gate source voltage to the FETs. The statements at page 6, lines 3-19 of the Office Action mailed December 7, 2009 are incorrect for the reasons stated above.

26. The declarant declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful and false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: August 3, 2010

Peter Fromherz
Dr. Peter Fromherz